Clinical trial results:
A Single Arm, Multi-Center, International, Continuation Trial of Recombinant Humanized Antibody Herceptin® (Trastuzumab) in Patients with HER2-Overexpressing Tumors

Summary

EudraCT number	2007-000348-28
Trial protocol	DE PT FR
Global end of trial date	11 February 2015

Results information

Result version number	v1 (current)
This version publication date	01 November 2019
First version publication date	01 November 2019

Trial information

Trial identification

Sponsor protocol code	BO15943

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02721641
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the study were to provide Herceptin IV to subjects with HER2-overexpressing disease following completion of any global Roche sponsored Herceptin study; to follow long-term outcomes in subjects who were being treated with Herceptin IV; and to follow long-term overall safety with Herceptin.

Protection of trial subjects:

All subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 1999
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	7 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Panama: 1
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	China: 3
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Guatemala: 1

Worldwide total number of subjects	69
EEA total number of subjects	33

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	45
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects with any indication who had, at least, stable disease while receiving Herceptin intravenous (IV) at the end of the lead-in study were eligible for this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Herceptin

Arm description:

Subjects received intravenous (IV) Herceptin until disease progression, unacceptable toxicity, death, or decision by the investigator or subject to discontinue treatment. Herceptin was administered at the discretion of the investigator as either 2 milligrams per kilogram (mg/kg) once weekly (first dose as a 4-mg/kg loading dose) or 6 mg/kg every 3 weeks (first dose as an 8-mg/kg loading dose) via IV infusion over 90 minutes.

Arm type	Experimental
Investigational medicinal product name	Herceptin
Investigational medicinal product code	
Other name	Trastuzumab
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV Herceptin until disease progression, unacceptable toxicity, death, or decision by the investigator or subject to discontinue treatment. Herceptin was administered at the discretion of the investigator as either 2 mg/kg once weekly (first dose as a 4-mg/kg loading dose) or 6 mg/kg every 3 weeks (first dose as an 8-mg/kg loading dose) via IV infusion over 90 minutes.

Number of subjects in period 1	Herceptin
Started	69
Completed	0
Not completed	69
Death	1
Refused Treatment	3
Drug Commercially Available	12
Not Specified	15
Adverse Event/Intercurrent Illness	1
Withdrawal by Subject	1
Lost to follow-up	1
Insufficient Therapeutic Response	35

Baseline characteristics

Reporting groups	
Reporting group title	Herceptin
Reporting group description:	
Subjects received intravenous (IV) Herceptin until disease progression, unacceptable toxicity, death, or decision by the investigator or subject to discontinue treatment. Herceptin was administered at the discretion of the investigator as either 2 milligrams per kilogram (mg/kg) once weekly (first dose as a 4-mg/kg loading dose) or 6 mg/kg every 3 weeks (first dose as an 8-mg/kg loading dose) via IV infusion over 90 minutes.	

Reporting group values	Herceptin	Total	
Number of subjects	69	69	
Age categorical			
Units: Subjects			

Age Continuous			
Age was the only demographic variable collected for the study and was only collected from 32 subjects.			
Units: years			
arithmetic mean	58.0		
standard deviation	± 11.00	-	
Gender, Customized			
Gender data were not collected. To submit results, additional estimated data were entered.			
Units: Subjects			
Female	69	69	
Male	0	0	

End points

End points reporting groups

Reporting group title	Herceptin

Reporting group description:

Subjects received intravenous (IV) Herceptin until disease progression, unacceptable toxicity, death, or decision by the investigator or subject to discontinue treatment. Herceptin was administered at the discretion of the investigator as either 2 milligrams per kilogram (mg/kg) once weekly (first dose as a 4-mg/kg loading dose) or 6 mg/kg every 3 weeks (first dose as an 8-mg/kg loading dose) via IV infusion over 90 minutes.

Primary: On-Study Duration on Trial Treatment

End point title	On-Study Duration on Trial Treatment[1]

End point description:

Analysis was performed on all enrolled subjects

End point type	Primary

End point timeframe:

From date of enrollment until death or premature withdrawal (maximum 7.4 years of follow-up)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analyses were performed for this end point.

End point values	Herceptin			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: days				
median (full range (min-max))	386.0 (1 to 2697)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Drop in Left Ventricular Ejection Fraction (LVEF) Below 45 Percent (%)

End point title	Number of Subjects with Drop in Left Ventricular Ejection Fraction (LVEF) Below 45 Percent (%)[2]

End point description:

All enrolled subjects with available LVEF data were included in the analysis.

End point type	Primary

End point timeframe:

From date of enrollment until disease progression, death, or premature withdrawal; assessed per investigator discretion (maximum 7.4 years of follow-up)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analyses were performed for this end point.

End point values	Herceptin			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Withdrawn from Study Because of LVEF Dysfunction

End point title	Number of Subjects Withdrawn from Study Because of LVEF Dysfunction[3]

End point description:

LVEF dysfunction was defined as low LVEF measured on two consecutive assessments, with the second assessment performed after 3 weeks of study medication being withheld. Low LVEF included values less than or equal to 39% or values between 40% and 45% (inclusive) with a decrease of 10 or more percentage points from Baseline. All enrolled subjects with available LVEF data were included in the analysis.

End point type	Primary

End point timeframe:

From date of enrollment until death or premature withdrawal (maximum 7.4 years of follow-up)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analyses were performed for this end point.

End point values	Herceptin			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From date of enrollment until disease progression, unacceptable toxicity, death, or decision by the investigator or subject to discontinue treatment (up to approximately 7.4 years)

Adverse event reporting additional description:

Only serious adverse events were collected during the trial. Terms were reported verbatim as provided by the reporter and were not re-coded. Analysis was performed on all enrolled subjects.

Assessment type	Non-systematic

Dictionary used

Dictionary name	Global Database
Dictionary version	N/A

Reporting groups

Reporting group title	Herceptin

Reporting group description:

Subjects received IV Herceptin until disease progression, unacceptable toxicity, death, or decision by the investigator or subject to discontinue treatment. Herceptin was administered at the discretion of the investigator as either 2 mg/kg once weekly (first dose as a 4-mg/kg loading dose) or 6 mg/kg every 3 weeks (first dose as an 8-mg/kg loading dose) via IV infusion over 90 minutes.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: This study did not collect non-serious adverse event information.

Serious adverse events	Herceptin		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 69 (15.94%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Pain management			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Herceptin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 69 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 1998	The protocol was updated to reflect a change from subjects with HER2-overexpressing breast cancer to subjects with HER2-overexpressing tumours as a result of the expansion of the development program for Herceptin; and no further chemotherapy was allowed to be taken concomitantly with Herceptin.
18 October 2000	The protocol was updated with all product-related information according to the Summary of Product Characteristics as a result of the approval of Herceptin in August 2000 by the European Agency for the Evaluation of Medicinal Products, including the possibility for subjects to receive paclitaxel in combination with Herceptin; participation in the study was limited to subjects with breast cancer; the dosing regimen was updated to include details for subjects who were receiving Herceptin IV in the lead-in protocol and subjects who were not previously treated with Herceptin IV.
12 February 2007	The protocol was updated as follows: subjects from all global Roche-sponsored Herceptin trial (all indications) were able to enroll into the study and would be provided with Herceptin even if it was commercially available in their country; subjects could continue treatment with the same anticancer drugs, at the same dose and schedule, they received in the lead-in protocol, as long as the treatment was still ongoing at the completion of the lead-in protocol and was still considered beneficial for the subject; the informed consent form was amended to include safety information relating to possible effects on reproduction or fetal development, risks and side effects, and the addition of regular heart function monitoring; the case report form (CRF) was changed to include date of visit, date of birth, and concomitant cancer treatments; left ventricular ejection fraction (LVEF) values were to be collected; the study completion page of the CRF was changed; the study completion date was replaced by date of last dose, date of progression, and date of death; the units of initial dose was changed from mg/kg to mg.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Age data were only collected for 22 subjects aged 18−64 yrs. and 10 subjects aged 65−84 yrs. Gender data were not collected. To submit results, additional estimated data were entered in the "Trial Information" and "Gender" sections.

Notes: